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Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma in the Multiethnic Cohort Study

Jongeun Rhee [a,1], Vicky C. Chang [a,1], Iona Cheng [b], Antonia M. Calafat [c], Julianne Cook Botelho [c], Joseph J. Shearer [d], Joshua N. Sampson [e], Veronica Wendy Setiawan [f], Lynne R. Wilkens [g], Debra T. Silverman [a], Mark P. Purdue [a,2], Jonathan N. Hofmann [a,2,*]

[a] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA
[b] Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA
[c] Organic Analytical Toxicology Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA, USA
[d] Heart Disease Phenomics Laboratory, Epidemiology and Community Health Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, USA
[e] Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, MD, USA
[f] Department of Population and Public Health Sciences and Norris Comprehensive Cancer Center, University of Southern California, CA, USA
[g] Population Sciences in the Pacific Program (Cancer Epidemiology), University of Hawaii Cancer Center, Honolulu, HI, USA

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) are environmentally persistent organic pollutants detectable in the serum of most U.S. adults. We previously reported a positive association between serum perfluorooctanoate (PFOA) concentrations and risk of renal cell carcinoma (RCC) within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, comprising predominantly White individuals enrolled in 1993–2001. To extend our investigations to a larger and more racially and ethnically diverse population, we conducted a nested case-control study of serum PFAS concentrations and RCC within the Multiethnic Cohort Study. We measured pre-diagnostic serum concentrations of nine PFAS among 428 RCC cases and 428 individually matched controls. We estimated odds ratios (ORs) and 95 % confidence intervals (CIs) for risk of RCC in relation to each PFAS using conditional logistic regression, adjusting for RCC risk factors and other PFAS. PFOA was not associated with RCC risk overall [doubling in serum concentration, $OR_{continuous} = 0.89$ (95 %CI = 0.67, 1.18)]. However, we observed suggestive positive associations among White participants [2.12 (0.87, 5.18)] and among participants who had blood drawn before 2002 [1.49 (0.77, 2.87)]. Furthermore, higher perfluorononanoate (PFNA) concentration was associated with increased risk of RCC overall [fourth vs. first quartile, OR = 1.84 (0.97, 3.50), $P_{trend} = 0.04$; $OR_{continuous} = 1.29$ (0.97, 1.71)], with the strongest association observed among African American participants [$OR_{continuous} = 3.69$ (1.33, 10.25)], followed by Native Hawaiian [2.24 (0.70, 7.19)] and White [1.98 (0.92, 4.25)] participants. Most other PFAS were not associated with RCC. While PFOA was not associated with RCC risk overall in this racially and ethnically diverse population, the positive associations observed among White participants and those with sera collected before 2002 are consistent with previous PLCO findings. Our study also

Abbreviations: EtFOSAA, 2-N-ethyl-perfluorooctane sulfonamido acetate; MeFOSAA, 2-N-methyl-perfluorooctane sulfonamido acetate; BMI, Body mass index; Cis, Confidence intervals; eGFR, Estimated glomerular filtration rate; IARC, International Agency for Research on Cancer; ICD-O-3, International Classification of Diseases for Oncology Third Revision; LOD, Limit of detection; n-PFOS, Linear perfluorooctane sulfonate; n-PFOA, Linear perfluorooctanoate; MEC, Multiethnic Cohort Study; NCI, National Cancer Institute; NHANES, National Health and Nutrition Examination Survey; NHPI, Native Hawaiians and Pacific Islanders; ORs, Odds ratios; PFAS, Per- and polyfluoroalkyl substances; PFDA, Perfluorodecanoate; PFHxS, Perfluorohexane sulfonate; PFNA, Perfluorononanoate; FOSA, Perfluorooctane sulfonamide; PFOS, Perfluorooctane sulfonate; PFOA, Perfluorooctanoate; PFUnDA, Perfluoroundecanoate; PLCO, Prostate, Lung, Colorectal and Ovarian; QC, Quality control; Sb-PFOA, Sum of branched perfluorooctanoate isomers; Sm-PFOS, Sum of perfluoromethylheptane sulfonic acid isomers.

* Corresponding author at: Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA.
E-mail address: hofmannjn@mail.nih.gov (J.N. Hofmann).
[1] Co-first authors.
[2] Co-senior authors.

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provided new evidence of a positive association between PFNA and RCC risk that was strongest in African American participants. These findings highlight the need for additional epidemiologic research investigating PFAS exposures and RCC in large racially and ethnically diverse populations.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of synthetic chemicals used since the 1940s in a broad range of industrial and consumer applications, such as nonstick cookware, food packaging, water-resistant fabric, cosmetics, and firefighting foams (Glüge et al., 2020). Despite decreased production of certain PFAS in the United States since the early 2000s, PFAS are highly persistent in the environment and remain ubiquitous contaminants of soil and water around the globe (Buck et al., 2011). Human exposure to PFAS occurs mainly via consumption of contaminated water and food and, to a lesser extent, inhalation of indoor air and dust and dermal contact (Sunderland et al., 2019). Once absorbed, some PFAS can accumulate in the human body over long periods of time, with serum elimination half-lives ranging from 2 to 8 years (Olsen et al., 2007; Li et al., 2018; Li et al., 2022). According to nationally representative data from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2008, > 95 % of the general U.S. population of 12 years of age or older had detectable concentrations of four major PFAS in their blood, including perfluorooctanoate (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA) (Calafat et al., 2007; Kato et al., 2011). Notably, serum concentrations of several PFAS have been found to differ by race and ethnicity. For example, elevated concentrations of PFOS and PFNA, especially in middle-aged or older populations, have been observed among non-Hispanic Black compared to non-Hispanic White persons in NHANES and other studies (Calafat et al., 2007; Kato et al., 2011; Park et al., 2019; Shearer et al., 2021). Data are more limited for other racial and ethnic groups; however, recent (since 2011) NHANES reports (Centers for Disease Control and Prevention) and a study in midlife women (Park et al., 2019) also reported higher serum PFNA concentrations among Asian American compared to non-Hispanic White individuals.

Given their widespread exposure and high environmental persistence, PFAS have emerged as a major public health concern worldwide, with a growing body of literature linking specific PFAS to adverse health outcomes, including cancer (National Academies of Sciences, Engineering, and Medicine, 2022; Steenland et al., 2020; Steenland and Winquist, 2021). In 2014, the International Agency for Research on Cancer (IARC) classified PFOA—the only PFAS evaluated by IARC to date—as "possibly carcinogenic to humans" (Group 2B) based in part on limited epidemiologic evidence of an association with kidney cancer (Benbrahim-Tallaa et al., 2014; International Agency for Research on Cancer, 2017). This conclusion was mainly drawn from studies that reported higher kidney cancer incidence or mortality among PFOA-exposed workers at a fluoropolymer production plant in West Virginia (Steenland and Woskie, 2012), and those residing in the surrounding communities who were highly exposed to PFOA through contaminated drinking water (Vieira et al., 2013; Barry et al., 2013). More recently, our group conducted the first prospective study to investigate associations between measured pre-diagnostic serum concentrations of PFAS, including PFOA and seven other PFAS, and risk of renal cell carcinoma (RCC; the most common form of kidney cancer) in a cohort with PFAS serum concentrations comparable to those observed in the general U.S. population (Shearer et al., 2021). In that nested case-control study of 324 RCC cases and 324 matched controls (89 % non-Hispanic White) within the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, we observed a statistically significant association between higher serum PFOA concentrations and increased RCC risk, including after adjustment for several other PFAS. We also observed positive associations with RCC risk for PFOS and PFHxS, although those associations were attenuated in mutually adjusted analyses. Importantly, our findings from the PLCO cohort provided evidence in support of PFOA as a renal carcinogen and demonstrated for the first time that general population exposures may contribute to RCC development. The incidence of RCC in the U.S. differs by race and ethnicity, with higher rates of disease in African American and American Indian / Alaskan Native populations than among non-Hispanic White Americans, while Latino and Asian and Pacific Islander populations experience lower rates (National Cancer Institute, 2023). In the current investigation, we sought to replicate our findings from PLCO in a larger and more racially and ethnically diverse population by conducting a nested case-control study to evaluate RCC risk in relation to pre-diagnostic serum concentrations of PFOA, PFOS, PFHxS, and six other PFAS in the Multiethnic Cohort Study (MEC).

2. Methods

2.1. Study population

Details of the MEC study design and data collection procedures have been described previously (Kolonel et al., 2000). Briefly, the MEC is a large racially, ethnically, and socioeconomically diverse prospective cohort of >215,000 men and women aged 45–75 years at baseline (1993–1996) from five different racial and ethnic groups (African Americans, 16 % of participants; Japanese Americans, 26 %; Latinos, 22 %; Native Hawaiians, 6 %; and Whites, 23 %) living in Hawaii and California (primarily Los Angeles County). Each participant completed a self-administered mailed questionnaire that inquired about demographic factors, anthropometric measures, personal behaviors, medical conditions including history of hypertension, diet, and family history of cancer. Assignment of study participants' race and ethnicity was based on their questionnaire responses (Kolonel et al., 2000). Incident cancers were identified through record linkages to the Surveillance, Epidemiology, and End Results Program's Hawaii Tumor Registry and the California State Cancer Registry.

Biospecimen collection in MEC first began in 1994 with cancer case-control studies, where samples were collected from cases after diagnosis and from a representative set of controls. Subsequently, from 2001 to 2006, the prospective MEC biorepository was created by asking surviving cohort members to provide blood and urine specimens (Park et al., 2009). The controls from the earlier studies and participants with sera in the prospective MEC biorepository were eligible for inclusion in the current study. Blood samples were processed within 4 h of collection, and aliquoted into 0.5-mL cryotubes that were stored in the vapor phase of liquid nitrogen (–186 °C). The majority of participants contributing to the biorepository provided fasting blood samples (~90 % for ≥ 10 h). The study was conducted in accordance with the Declaration of Helsinki; participants provided written informed consent for biospecimen collection, and the study protocol was approved by Institutional Review Boards at the University of Southern California and the University of Hawaii. De-identified samples and data were provided to National Cancer Institute (NCI) investigators and designated laboratories under a material transfer agreement between the NCI and the University of Hawaii and the University of Southern California. Analyses conducted by NCI and the designated laboratories did not constitute engagement in human subjects research given the de-identified nature of the transferred data and specimens.

2.2. Case and control selection

We included all incident cases of RCC with an available pre-diagnostic serum sample that were diagnosed through 2018. Incident RCC cases were defined as the International Classification of Diseases for Oncology, Third Revision (ICD-O-3) code C64.9, with the exclusion of transitional cell carcinomas (ICD-O-3 morphology codes 8120 and 8130). Controls were individually matched to cases with a 1:1 ratio on sex, race and ethnicity, study center (Hawaii, California), age at serum collection (±1 year), date of serum collection (±1 year), time of serum collection (±3 h), and fasting status (0-<6, 6-<8, 8-<10, ≥10 h). Matching criteria were gradually relaxed for a small subset (7 %) of the case-control pairs, with nearly all sets matched within 3 years for both age at serum collection and date of serum collection. Eligible controls were alive and free of RCC as of the age of diagnosis of their matched case. For each case and control, we selected one parent aliquot of serum. In total, 428 RCC cases and 428 controls (n = 856) were included for analysis.

2.3. PFAS and creatinine measurements

We measured serum concentrations of 11 PFAS: perfluorooctane sulfonamide (FOSA), 2-N-methyl-perfluorooctane sulfonamido acetate (MeFOSAA), 2-N-ethyl-perfluorooctane sulfonamido acetate (EtFOSAA), PFHxS, linear PFOS (n-PFOS), sum of perfluoromethylheptane sulfonic acid isomers (Sm-PFOS), linear PFOA (n-PFOA), sum of branched PFOA isomers (Sb-PFOA), PFNA, perfluorodecanoate (PFDA), and perfluoroundecanoate (PFUnDA). The limit of detection (LOD) was 0.1 μg/L for all PFAS; concentrations below the LOD were assigned a value of the LOD/$\sqrt{2}$ (0.071 μg/L). We calculated the concentrations of PFOA and PFOS by summing the concentrations of their respective isomers [i.e., PFOA (n-PFOA and Sb-PFOA) and PFOS (n-PFOS and Sm-PFOS)]. Serum PFAS concentrations were quantified at the Centers for Disease Control and Prevention (CDC, Atlanta, GA) using online solid-phase extraction coupled to high-performance liquid chromatography–isotope dilution-tandem mass spectrometry, as described previously (Kato et al., 2018). Samples from each matched case/control set were placed next to each other within the same batch. To evaluate measurement reproducibility, we included replicate quality control (QC) samples among batches (n = 96; ~11 % of the total number of test samples) from pooled serum from subjects recruited in Hawaii, selected to have similar distributions of race and ethnicity, age, and sex as the cases and controls. The QC samples were coded such that laboratory personnel were blinded to the replicates. All PFAS evaluated in this study had within-batch coefficients of variation ≤ 20 % except PFUnDA (21 %).

To address concerns that kidney function may affect serum PFAS concentrations and could potentially confound or modify the associations with RCC (Shankar et al., 2011; Jain & Ducatman, 2019; Dhingra et al., 2017), we also measured serum creatinine and calculated estimated glomerular filtration rate (eGFR) using the 2021 CKD-EPI creatinine equation (Inker et al., 2021).

2.4. Statistical analysis

As preliminary analyses, we calculated Spearman rank correlations between PFAS concentrations among controls and examined the distributions of participant characteristics by case-control status using chi-squared tests. We also estimated adjusted geometric least-squares mean concentrations of each PFAS across categories of participant characteristics [sex, race and ethnicity, study center, calendar year of blood draw, age at blood draw, fasting status, smoking status at baseline, body mass index (BMI) at or close to time of blood collection, history of hypertension at or close to blood collection, eGFR, and (among female participants) years since menopause] among controls (n = 428) using multivariable linear regression.

For our main analyses, we calculated odds ratios (ORs) and 95 % confidence intervals (CIs) for the risk of RCC in relation to serum concentrations of each PFAS using conditional logistic regression among the matched case-control pairs. PFAS were modeled both as continuous variables (log2-transformed) and across categories defined using quartiles of concentrations among controls as cut-points. For PFAS with ≥ 20 % non-detectable concentrations (EtFOSAA, PFUnDA), we assigned subjects with concentrations below the LOD as the referent group and created categories using control tertiles as cut-points. For FOSA, because 76 % of results were non-detectable, we created a binary variable (non-detectable, detectable) for the analysis. Linear trends across categories of each PFAS (except FOSA) were assessed using a Wald test by modelling within-category median concentrations as a continuous variable. In addition to conditioning on the matched factors, all models were adjusted for established RCC risk factors, including BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2, missing), eGFR (<60, 60-<90, ≥90 mL/min/1.73 m^2, missing), smoking status (never, former, current, missing), and history of hypertension (yes, no); missing values were assigned as separate categories. To assess independent associations of each PFAS with RCC risk, we performed analyses additionally adjusting for serum concentrations of other PFAS, including those with *a priori* evidence of associations in the PLCO investigation (log2-transformed concentrations of PFOA, PFOS, and PFHxS) (Shearer et al., 2021) and those found to be associated with RCC risk in the current investigation [PFNA (log2-transformed) and FOSA (non-detectable, detectable)].

We also conducted analyses stratified by matching factors [race and ethnicity (African American, Japanese American, Latino, Native Hawaiian, White), sex (male, female), study center (Hawaii, California), calendar year of blood draw (<2002, ≥2002; before and after the phaseout or decreased production of certain PFAS and subsequent declines in concentrations in the general U.S. population (Calafat et al., 2007), age at blood draw (<65, ≥65 years), and fasting status (<10, ≥10 h)], smoking status (never, ever), eGFR (<60, 60-<90, ≥90 mL/min/1.73 m^2), history of hypertension (no, yes), and BMI (<25, 25-<30, ≥30 kg/m^2) and evaluated statistical significance of multiplicative interactions using the Wald test for cross-product model terms. For analyses stratified by non-matching factors (smoking status, eGFR, history of hypertension, and BMI), we broke the matched case-control sets and fit unconditional logistic regression models adjusting for matching factors. We also investigated associations stratified by median years of follow-up (<7, ≥7 years) and restricted to clear cell RCC subtype. As sensitivity analyses, we restricted to RCC cases diagnosed > 2 years after the time of blood draw (376 cases and 376 controls) and participants without any history of cancer prior to blood collection (353 cases and 351 controls). We also repeated analyses restricting to participants with no missing data on BMI, smoking, and/or eGFR (404 cases and 404 controls). Lastly, we conducted analyses restricting to post-menopausal women with > 10 years since menopause at blood collection (127 cases and 133 controls) as menstruation has been related to serum PFAS concentrations. (Rickard et al., 2022) All statistical analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC) and RStudio Version 1.3.1093 (https://www.rstudio.com/). All statistical tests were two-sided.

3. Results

Selected characteristics of the RCC cases and controls are presented in Table 1. Participants were racially and ethnically diverse (African American 17 %, Japanese American 25 %, Latino 27 %, Native Hawaiian 12 %, White 19 %), with a median age at blood draw of 67 years. The majority of participants were male (63 %), provided serum in 2002 or later (79 %), and had fasted for ≥ 10 h prior to blood collection (85 %). Nearly all female participants (99 %) were post-menopausal at blood collection and 87 % of them became menopausal at least 10 years before blood draw. Cases were more likely to be overweight or obese and have a history of hypertension compared to controls (P = 0.03 and 0.002, respectively). Nearly 30 % of study participants had impaired kidney

Table 1
Selected characteristics [n (%)] of renal cell carcinoma cases and controls in the Multiethnic Cohort Study.

Characteristic	Controls (n = 428)		Cases (n = 428)		P
Sex					
Male	268	(62.6)	268	(62.6)	—
Female	160	(37.4)	160	(37.4)	
Race and ethnicity					
African American	72	(16.8)	72	(16.8)	—
Japanese American	107	(25.0)	107	(25.0)	
Latino	116	(27.1)	116	(27.1)	
Native Hawaiian	50	(11.7)	50	(11.7)	
White	80	(18.7)	80	(18.7)	
Other[b]	3	(0.7)	3	(0.7)	
Study center					
Hawaii	211	(49.3)	211	(49.3)	—
California	217	(50.7)	217	(50.7)	
Age at blood draw, years					
<60	82	(19.2)	82	(19.2)	—
60 to < 65	92	(21.5)	93	(21.7)	
65 to < 70	91	(21.3)	89	(20.8)	
70 to < 75	86	(20.1)	88	(20.6)	
≥75	77	(18.0)	76	(17.8)	
Calendar year of blood draw					
1994–2001	91	(21.3)	91	(21.3)	—
2002	50	(11.7)	79	(18.5)	
2003	122	(28.5)	112	(26.2)	
2004	106	(24.8)	87	(20.3)	
2005–2006	59	(13.8)	59	(13.8)	
Fasting status, hours					
<10	63	(14.7)	63	(14.7)	—
≥10	365	(85.3)	365	(85.3)	
History of hypertension[d]					
No	229	(53.5)	183	(42.8)	**0.002**
Yes	199	(46.5)	245	(57.2)	
Body mass index[e], kg/m^2					
<18.5	9	(2.1)	2	(0.5)	**0.03**
18.5 to < 25	139	(32.5)	113	(26.4)	
25 to < 30	165	(38.6)	194	(45.3)	
≥30	114	(26.6)	117	(27.3)	
Unknown	1	(0.2)	2	(0.5)	
Cigarette smoking status[d]					
Never	174	(40.7)	188	(43.9)	0.71
Former	181	(42.3)	175	(40.9)	
Current	65	(15.2)	56	(13.1)	
Unknown	8	(1.9)	9	(2.1)	
eGFR, mL/min/1.73 m^2					
<60	116	(27.1)	124	(29.0)	0.85
60-<90	257	(60.0)	244	(57.0)	
≥90	52	(12.1)	57	(13.3)	
Unknown	3	(0.7)	3	(0.7)	

Abbreviations: eGFR, estimated glomerular filtration rate.
Bold indicates statistical significance at P < 0.05.
[a] *P*-value for difference between cases and controls, calculated using chi-squared test for history of hypertension and smoking status and Fisher's exact test for body mass index and eGFR. Not reported for matching factors (sex, race and ethnicity, study center, age at blood draw, calendar year of blood draw, and fasting status).
[b] Includes Chinese, Filipino, Korean and other ethnic groups.
[c] Includes fasting < 10 h or unknown.
[d] Based on information reported at or close to time of blood draw.
[e] Reported at baseline.

function (eGFR < 60 mL/min/1.73 m^2), although no difference between cases and controls was observed.

PFHxS, PFOS, PFOA, and PFNA were detected in ≥ 97 % of participants samples. MeFOSAA, EtFOSAA, PFDA, and PFUnDA had non-detectable concentrations ranging from 15 to 30 %, and the majority of participants had non-detectable FOSA concentrations (76 %). The nine PFAS were moderately correlated with one another in pair-wise comparisons among controls (Supplementary Table S1); some of the strongest correlations were observed between PFNA and PFDA (ρ = 0.84) and PFUnDA (ρ = 0.64), PFOA-PFOS (ρ = 0.61), PFOA-PFNA (ρ = 0.57), and PFOS-PFHxS (ρ = 0.55).

Among controls, we observed that the adjusted geometric least-squares mean concentrations of PFOS, PFNA, PFDA, PFUnDA, and MeFOSAA significantly differed by race and ethnicity (Supplementary Table S2). Compared to White participants, African American and Native Hawaiian participants had higher PFOS, PFNA, PFDA, and MeFOSAA concentrations and Japanese American participants had higher PFNA, PFDA, and PFUnDA concentrations. PFAS concentrations among Latino participants were generally lower than in the other racial and ethnic groups. Concentrations of PFDA and PFUnDA were higher among participants recruited from Hawaii compared to those from California (P = 0.01 and 0.0001, respectively). We observed significant declining patterns of PFOS, MeFOSAA, and EtFOSAA by calendar year of blood draw, while concentrations of PFNA and PFDA increased slightly by calendar year (Supplementary Table S2). We observed higher PFAS concentrations among men in general and particularly for PFHxS (P = 0.003), PFOS (P = 0.02), and MeFOSAA (P = 0.03). In addition, concentrations of most PFAS except PFHxS and EtFOSAA decreased marginally by increasing age at blood draw. PFAS concentrations were similar across categories of eGFR, smoking, BMI, and hypertension.

In this population, PFOA was not associated with RCC risk overall, when serum concentrations were modelled categorically [fourth vs. first quartile, OR_{Q4} = 1.04 (95 % CI = 0.60, 1.81)] or continuously ([doubling in concentration, $OR_{continuous}$ = 0.89 (0.67, 1.18), Table 2]. However, we observed a suggestive positive association among White participants [$OR_{continuous}$ = 2.12 (0.87, 5.18), Table 3; ORs ranging from 2.1 to 3.6 for quartiles 2–4 vs. quartile 1, Supplementary Table S3] and among participants who provided their serum before 2002 [$OR_{continuous}$ = 1.49 (0.77, 2.87)], although differences by race and ethnicity ($P_{interaction}$ = 0.65) and calendar year ($P_{interaction}$ = 0.98) were not statistically significant. We also observed some evidence of heterogeneity across categories of eGFR ($P_{interaction}$ = 0.05), with a suggestive inverse association among those with impaired kidney function ([eGFR < 60, $OR_{continuous}$ = 0.59 (0.34, 1.01)] and non-significant positive associations among those with normal kidney function [e.g., for eGFR ≥ 90, $OR_{continuous}$ = 1.25 (0.39, 4.04); Table 3].

Furthermore, higher PFNA concentrations were associated with increased risk of RCC overall, with a statistically significant exposure–response trend [OR_{Q4} = 1.84 (0.97, 3.50), P_{trend} = 0.04; $OR_{continuous}$ = 1.29 (0.97, 1.71), Table 2], adjusting for RCC risk factors and other PFAS. The strongest association with PFNA was observed among African American participants [$OR_{continuous}$ = 3.69 (1.33, 10.25), Table 3], and we also observed elevated but non-statistically significant risk estimates among Native Hawaiian [$OR_{continuous}$ = 2.24 (0.70, 7.19)] and White [$OR_{continuous}$ = 1.98 (0.92, 4.25)] participants. Positive associations with PFNA were also most apparent among participants with blood drawn in 2002 or later [1.43 (1.01, 2.01); $P_{interaction}$ = 0.25, Table 3], those with blood samples collected < 7 years prior to diagnosis [1.58 (1.04, 2.41); $P_{interaction}$ = 0.86], and those who fasted for ≥ 10 h [1.58 (1.15, 2.17); $P_{interaction}$ = 0.005, Supplementary Table S4]. Patterns of associations with PFNA overall and by race and ethnicity were similar after further adjustment for additional PFAS that were correlated with PFNA concentrations (PFDA and PFUnDA; Supplementary Table S5).

We also observed a positive association for FOSA (detectable vs. non-detectable) overall [OR = 1.78 (1.05, 3.04), Table 2] after adjustment for other PFAS. This association was only evident among women [11.72

Table 2
Odds ratios (ORs) and 95 % confidence intervals (CIs) evaluating PFAS serum concentrations and risk of renal cell carcinoma in the Multiethnic Cohort Study.

PFAS (μg/L)	N control	N case	OR (95 % CI)	OR (95 % CI)
PFOA				
≤3.27	106	107	1	1
>3.27–4.47	102	99	1.09 (0.73,1.64)	1.26 (0.80,1.97)
>4.47–6.22	113	122	1.05 (0.70,1.56)	1.26 (0.78,2.05)
>6.22	107	100	0.88 (0.58,1.35)	1.04 (0.60,1.81)
P-trend			0.46	0.75
Continuous	428	428	0.87 (0.73,1.05)	0.89 (0.67,1.18)
PFOS				
<16.65	107	118	1	1
16.65-<25.05	107	105	0.90 (0.60,1.35)	1.05 (0.66,1.66)
25.05-<36.40	106	100	0.89 (0.57,1.37)	0.99 (0.58,1.68)
≥36.40	108	105	0.83 (0.53,1.30)	0.93 (0.51,1.72)
P-trend			0.44	0.72
Continuous	428	428	0.92 (0.79,1.07)	0.95 (0.74,1.23)
PFHxS				
<1.6	105	121	1	1
1.6-<2.4	103	116	0.94 (0.64,1.38)	0.97 (0.64,1.49)
2.4-<3.55	113	88	**0.65 (0.44,0.98)**	0.67 (0.43,1.06)
≥3.55	107	103	0.79 (0.52,1.21)	0.84 (0.50,1.41)
P-trend			0.27	0.54
Continuous	428	428	**0.84 (0.74,0.96)**	**0.82 (0.69,0.98)**
PFNA				
≤0.5	121	119	1	1
>0.5–0.8	120	113	0.88 (0.59,1.32)	1.13 (0.70,1.82)
>0.8–1.1	85	78	0.90 (0.57,1.42)	1.24 (0.71,2.16)
>1.1	102	118	1.29 (0.78,2.12)	1.84 (0.97,3.50)
P-trend			0.24	**0.04**
Continuous	428	428	1.03 (0.85,1.24)	1.29 (0.97,1.71)
PFDA				
≤0.1	121	128	1	1
>0.1–0.2	128	101	0.77 (0.52,1.14)	0.91 (0.57,1.46)
>0.2–0.4	106	119	1.15 (0.74,1.79)	1.37 (0.77,2.42)
>0.4	73	80	1.26 (0.75,2.14)	1.42 (0.70,2.89)
P-trend			0.24	0.26
Continuous	428	428	1.05 (0.88,1.24)	1.11 (0.85,1.43)
PFUnDA				
<LOD (non-detectable)	111	130	1	1
0.1–0.2	139	118	0.75 (0.50,1.13)	0.75 (0.48,1.17)
>0.2–0.4	77	66	0.75 (0.43,1.31)	0.79 (0.42,1.48)
>0.4	101	114	1.05 (0.61,1.82)	0.88 (0.45,1.72)
P-trend			0.34	0.80
Continuous	428	428	0.97 (0.84,1.12)	0.90 (0.75,1.08)
MeFOSAA				
≤0.3	117	118	1	1
>0.3–0.6	114	103	0.93 (0.63,1.36)	0.94 (0.64,1.40)
>0.6–1.1	96	104	1.07 (0.71,1.63)	1.13 (0.73,1.74)
>1.1	101	103	1.16 (0.74,1.81)	1.22 (0.76,1.97)
P-trend			0.42	0.34
Continuous	428	428	1.00 (0.88,1.13)	1.00 (0.87,1.14)
EtFOSAA				
<LOD (non-detectable)	100	90	1	1
0.1-<0.3	102	112	1.16 (0.76,1.76)	1.15 (0.75,1.78)
0.3-<0.7	112	104	1.07 (0.66,1.72)	1.12 (0.67,1.86)
≥0.7	114	122	1.35 (0.76,2.37)	1.35 (0.73,2.49)
P-trend			0.34	0.40
Continuous	428	428	1.03 (0.92,1.16)	1.03 (0.90,1.18)

(continued on next page)

Table 2 (*continued*)

PFAS (μg/L)	N control	N case	OR (95 % CI)	OR (95 % CI)
FOSA				
Non-detectable	331	319	1	1
Detectable	95	107	1.58 (0.95,2.60)	**1.78 (1.05,3.04)**

Abbreviations: EtFOSAA, 2-N-ethyl-perfluorooctane sulfonamido acetate; FOSA, perfluorooctane sulfonamide; MeFOSAA, 2-N-methyl-perfluorooctane sulfonamido acetate; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoate; eGFR, estimated glomerular filtration rate.
Bold indicates statistical significance at $P < 0.05$.

[a] Analyses were conducted using conditional logistic regression models of matched case-control sets adjusting for smoking status (never, former, current, missing), body mass index (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2, missing), history of hypertension (yes, no), and eGFR (<60, 60-<90, ≥90 mL/min/1.73 m^2, missing).

[b] Additionally adjusted for serum concentrations of PFOA (log2-transformed), PFOS (log2-transformed), PFHxS (log2-transformed), PFNA (log2-transformed), and FOSA (non-detectable, detectable, missing).

[c] PFOA and PFOS here represent the sum of their corresponding linear and branch isomers.

[d] Continuous odds ratios (95 % confidence intervals) for renal cell carcinoma in relation to a 1-unit increase in serum PFAS concentrations on the log base 2 scale, corresponding to a doubling in analyte concentrations.

[e] FOSA analysis was conducted using 426 cases and 426 controls because of missing FOSA measurements [1 case and 1 control; we additionally excluded their respective matched control (n = 1) and case (n = 1) for conditional logistic regression].

(2.84, 48.38) vs. 1.04 (0.56, 1.94) among men; $P_{interaction} = 0.005$, Table 3]. An inverse association with RCC risk was found for continuous concentrations of PFHxS overall [$OR_{continuous} = 0.82$ (0.69, 0.98), Table 2] and particularly among Latino individuals [0.64 (0.42, 0.99); $P_{interaction} = 0.84$, Table 3] and individuals aged < 65 years at blood draw [0.69 (0.51, 0.94); $P_{interaction} = 0.03$]. Other PFAS were not associated with RCC overall (Table 2), although for PFOS we observed a suggestive positive association in Japanese American participants [$OR_{continuous} = 1.54$ (0.91, 2.62), Table 3] and statistically significant inverse associations among African American [0.40 (0.20, 0.79)] and White [0.36 (0.13, 0.95); $P_{interaction} = 0.18$] participants.

We observed no statistically significant differences in associations by other stratifying factors, including hypertension, smoking status, and BMI (Supplementary Table S4). In addition, we observed similar results in sensitivity analyses restricting to RCC cases diagnosed > 2 years after serum collection, participants without any history of cancer prior to blood collection, participants with no missing data on BMI, smoking, and/or eGFR, and post-menopausal women with > 10 years since menopause at blood collection.

4. Discussion

In this nested case-control study of 428 cases and 428 matched controls from a racially and ethnically diverse population-based cohort from Hawaii and California, we found no association between pre-diagnostic serum PFOA concentrations and RCC risk overall. However, we observed suggestive associations between higher PFOA concentrations and increased RCC risk among White participants and among individuals with pre-diagnostic serum samples collected prior to year 2002; such observations are notable because our previous study within the PLCO cohort consisted of a predominantly non-Hispanic White population enrolled in 1993–2001 (Shearer et al., 2021). In the current study, we also observed a suggestive positive association between serum PFNA concentrations and RCC risk overall, particularly in analyses adjusted for other PFAS. Race and ethnicity-specific analyses for PFNA further revealed a statistically significant positive association with RCC risk among African American participants and positive but non-statistically significant associations among Native Hawaiian and White participants. Furthermore, participants with detectable serum concentrations of FOSA, a precursor of PFOS (Benskin et al., 2009; Xu et al., 2004), had a statistically significantly elevated risk of RCC compared to those with non-detectable FOSA concentrations. In stratified analyses, this association was only apparent in women. Finally, we found an inverse association between continuous serum concentrations of PFHxS and RCC risk overall and no associations overall for PFOS or other PFAS.

Serum concentrations of PFAS among controls in our study, overall and by demographic factors such as sex and age, are generally within the ranges observed in NHANES during a similar time period (Calafat et al., 2007; Kato et al., 2011; Centers for Disease Control and Prevention), suggesting that exposures among MEC participants reflect exposures experienced by the general U.S. population. Consistent with other studies (Calafat et al., 2007; Kato et al., 2011; Park et al., 2019; Shearer et al., 2021; Centers for Disease Control and Prevention), we observed racial and ethnic differences in concentrations of several PFAS, even after accounting for study site and other factors potentially related to PFAS concentrations. Notably, African American and Native Hawaiian participants had the highest concentrations of PFOS, while African American, Japanese American, and Native Hawaiian participants had higher concentrations of PFNA relative to Latino and White participants. Similar to our findings in this older population, elevated concentrations of PFOS and PFNA have also been observed among non-Hispanic Black individuals aged ≥ 55 years compared to non-Hispanic White individuals and Mexican Americans in NHANES (Calafat et al., 2007), and among Black (vs. White) control participants (ages ≥ 55 years) in PLCO (Shearer et al., 2021). Likewise, PFNA concentrations were elevated among Japanese American (vs. White) women in a multiethnic study of middle-aged women across the U.S. (Park et al., 2019) and among Asian Americans (all ethnicities combined) in NHANES (Centers for Disease Control and Prevention). Little is known about PFAS exposure among Native Hawaiian and Pacific Islander (NHPI) populations; the higher concentrations observed among Native Hawaiian participants in our study warrant further investigation in larger samples of this population. Racial and ethnic differences in PFAS concentrations likely reflect differences in sources of exposure, including drinking water supply, dietary consumption (e.g., packaged foods, fish/shellfish), and consumer product use (Park et al., 2019; Borrow et al., 2019; Obeng-Gyasi, 2022; Nelson et al., 2012). Future research investigating race and ethnicity-specific determinants of PFAS concentrations is needed to better understand these disparities and identify potentially modifiable factors for reducing exposure.

The previously observed association between PFOA and RCC risk in the PLCO cohort (Shearer et al., 2021) was not replicated overall in our current investigation within MEC. Differences between these two cohorts, particularly in the racial and ethnic distributions and time periods of blood collection, may have contributed to this discrepancy. While most participants in PLCO were non-Hispanic White (89 %; vs. 6 % Black and 5 % other) (Shearer et al., 2021), the MEC targeted recruitment from five main racial and ethnic groups (African American, Japanese American, Latino, Native Hawaiian, and White) (Kolonel et al., 2000), with Latino and Japanese Americans together comprising ~50 % of all

participants in this study. Notably, when analyses were restricted to White participants (19 %), we observed a greater than two-fold increase in RCC risk associated with a doubling in serum PFOA concentration; despite a lack of statistical significance, the magnitude of this association is similar, and even slightly stronger, compared to that in PLCO (OR = 1.7) (Shearer et al., 2021). In contrast, we found no evidence of an association among each of the other racial and ethnic groups. Racial and ethnic variations in exposure sources and pathways could have played a role in the RCC association, with higher serum PFOA concentrations noted among non-Hispanic White compared to other groups in several studies (Nato et al., 2011; Park et al., 2019; Boronow et al., 2019); however, our data did not reveal such a difference. To our knowledge, this was the first study to evaluate the PFOA–RCC association by race and ethnicity and among non-White individuals. Additional research in both White and other specific racial and ethnic groups may help clarify whether this association is most relevant among White individuals and whether the results are generalizable to other populations. Furthermore, nearly 80 % of participants in this study had blood drawn in 2002 or

Table 3
Odds ratios (ORs)[a] and 95 % confidence intervals (CIs) evaluating PFAS serum concentrations and risk of renal cell carcinoma stratified by selected characteristics in the Multiethnic Cohort Study.

Characteristic	N controls	N cases	PFOA[b]	PFOS[b]	PFHxS	PFNA	FOSA
All	428	428	0.89 (0.67,1.18)	0.95 (0.74,1.23)	**0.82 (0.69,0.98)**	1.29 (0.97,1.71)	**1.78 (1.05,3.04)**
Race and ethnicity							
African American	72	72	1.01 (0.51,1.98)	**0.40 (0.20,0.79)**	0.70 (0.38,1.31)	**3.69 (1.33,10.25)**	1.05 (0.26,4.19)
Japanese	107	107	1.00 (0.47,2.13)	1.54 (0.91,2.62)	0.69 (0.47,1.01)	0.82 (0.41,1.61)	2.28 (0.56,9.29)
Latino	116	116	1.04 (0.53,2.03)	1.30 (0.68,2.49)	**0.64 (0.42,0.99)**	1.03 (0.56,1.89)	2.05 (0.63,6.66)
Native Hawaiian	50	50	0.57 (0.21,1.55)	0.59 (0.20,1.73)	1.05 (0.59,1.88)	2.24 (0.70,7.19)	6.69 (0.86,51.9)
White	80	80	2.12 (0.87,5.18)	**0.36 (0.13,0.95)**	0.83 (0.56,1.23)	1.98 (0.92,4.25)	1.35 (0.38,4.83)
P-interaction[c]			0.65	0.18	0.84	0.96	0.81
Sex							
Male	268	268	1.05 (0.72,1.53)	0.94 (0.67,1.34)	0.80 (0.64,1.02)	1.22 (0.84,1.76)	1.04 (0.56,1.94)
Female	160	160	0.67 (0.39,1.12)	0.95 (0.60,1.49)	0.80 (0.58,1.09)	1.59 (0.96,2.63)	**11.72 (2.84,48.38)**
P-interaction			0.65	0.89	0.97	0.81	**0.005**
Study center							
Hawaii	211	211	0.96 (0.61,1.49)	0.92 (0.63,1.36)	0.88 (0.70,1.11)	1.31 (0.88,1.95)	1.65 (0.79,3.47)
California	217	217	0.88 (0.60,1.31)	0.94 (0.65,1.35)	**0.75 (0.56,0.99)**	1.31 (0.86,2.00)	1.97 (0.89,4.34)
P-interaction			0.29	0.41	0.17	0.55	0.78
Calendar year of blood draw[d]							
<2002	90	90	1.49 (0.77,2.87)	0.77 (0.40,1.48)	0.67 (0.42,1.06)	0.89 (0.49,1.62)	1.06 (0.36,3.08)
≥2002	336	336	0.80 (0.56,1.13)	0.96 (0.73,1.28)	0.85 (0.70,1.03)	**1.43 (1.01,2.01)**	**2.48 (1.19,5.16)**
P-interaction			0.98	0.52	0.42	0.25	0.17
Age at blood draw[d], years							
<65	170	170	0.84 (0.51,1.41)	0.97 (0.59,1.57)	**0.69 (0.51,0.94)**	1.22 (0.72,2.07)	**2.84 (1.01,8.04)**
≥65	249	249	0.92 (0.63,1.33)	0.94 (0.68,1.29)	0.95 (0.76,1.19)	1.30 (0.91,1.84)	1.51 (0.77,2.96)
P-interaction			0.32	0.30	**0.03**	0.28	0.88
Years of follow-up							
<7	206	206	0.86 (0.57,1.31)	0.74 (0.52,1.05)	0.88 (0.69,1.13)	**1.58 (1.04,2.41)**	**2.73 (1.19,6.30)**
≥7	222	222	0.91 (0.60,1.37)	1.28 (0.84,1.94)	**0.73 (0.56,0.96)**	1.11 (0.75,1.64)	1.26 (0.61,2.61)
P-interaction			0.66	0.23	0.85	0.86	0.41
eFER[e] mL/min/1.73 m^2							
<60	116	124	0.59 (0.34,1.01)	0.97 (0.58,1.64)	0.93 (0.68,1.27)	1.53 (0.90,2.59)	1.73 (0.84,3.57)
60-<90	257	244	1.11 (0.77,1.60)	0.97 (0.68,1.38)	0.82 (0.65,1.03)	**1.43 (1.03,1.97)**	1.19 (0.72,1.96)
≥90	52	57	1.25 (0.39,4.04)	0.51 (0.20,1.35)	0.56 (0.26,1.20)	1.53 (0.53,4.42)	2.02 (0.50,8.26)
P-interaction			0.05	0.13	0.10	0.54	0.88

Abbreviations: eGFR, estimated glomerular filtration rate, FOSA, perfluorooctane sulfonamide; PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate.
Bold indicates statistical significance at $P < 0.05$.

[a] Unless otherwise specified, analyses were conducted using conditional logistic regression models of matched case-control sets adjusting for smoking status (never, former, current, missing), body mass index (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2, missing), history of hypertension (yes, no), eGFR (<60, 60-<90, ≥90 mL/min/1.73 m^2, missing), PFOA (log2-transformed), PFOS (log2-transformed), PFHxS (log2-transformed), PFNA (log2-transformed), FOSA (non-detectable, detectable, missing). Continuous odds ratios (95 % confidence intervals) for renal cell carcinoma in relation to a 1-unit increase in serum PFAS concentrations on the log base 2 scale, corresponding to a doubling in analyte concentrations. For FOSA analysis, ORs for detectable FOSA vs. non-detectable FOSA are presented.

[b] PFOA and PFOS here represent the sum of their corresponding linear and branch isomers.

[c] P-value for multiplicative interaction evaluated using the Wald test for a cross-product term between PFAS and stratifying factor.

[d] For analysis of calendar year of blood draw and age at blood draw, unmatched sets were excluded from the analysis (n = 4 and n = 18, respectively).

[e] Analyses were conducted using unconditional logistic regression models adjusting for matching factors [sex, race and ethnicity (African American, Japanese, Latino, Native Hawaiian, White, other), study center (Hawaii, California), calendar year of blood draw (1994–2001, 2002, 2003, 2004, 2005–2006), age at blood draw (<60, 60-<65, 65-<70, 70-<75, ≥75 years), fasting status (≥10 hours, <10 hours or missing)], smoking status (never, former, current, missing), body mass index (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2, missing), history of hypertension (yes, no), eGFR (<60, 60-<90, ≥90 mL/min/1.73 m^2, missing), PFOA (log2-transformed), PFOS (log2-transformed), PFHxS (log2-transformed), PFNA (log2-transformed), and FOSA (non-detectable, detectable, missing).

later (i.e., after the phaseout of certain PFAS), which likely explains the generally lower PFAS concentrations than those observed in PLCO. In fact, although suggestive, our finding for PFOA and RCC risk among those with sera collected before 2002 is consistent with the association observed in PLCO (Shearer et al., 2021). In addition to the generally higher serum PFOA concentrations that were observed in the general U. S. population during this time period (Calafat et al., 2007), it is possible that the measured PFOA concentrations among these participants in our study could also reflect more stable estimates of longer-term PFOA exposure relative to those with later serum collections when PFOA concentrations were declining in the U.S. population overall. Future studies that can evaluate associations between PFOA and RCC in populations with a wider range of serum concentrations and with exposures assessed during different secular time periods may help to clarify these relationships. Another difference between the MEC and PLCO study populations is the higher prevalence of eGFR < 60 in MEC compared with PLCO (28 % vs. 7 %), which may be attributable in part to the older age at blood draw in MEC than PLCO (≥ 65 years: 59 % vs. 36 %, respectively). We note that there was some evidence of heterogeneity in our findings for PFOA by eGFR category, with a suggestive inverse association among participants with eGFR < 60 and non-significant positive associations in those with higher eGFR.

Our investigations within the PLCO (Shearer et al., 2021) and MEC cohorts are, to our knowledge, the only studies to date to assess directly measured serum PFOA (and other PFAS) concentrations in relation to kidney cancer risk in the general population. Other epidemiologic studies, including those cited in IARC's previous evaluation of PFOA, have been conducted in occupational settings or in highly exposed communities (Steenland & Winquist, 2021; International Agency for Research on Cancer, 2017; Barrett & Vieira, 2021). In a study of workers from a PFOA-producing chemical plant in West Virginia, an excess in deaths from kidney cancer was observed among those with high model-estimated cumulative serum PFOA concentrations (Steenland & Woskie, 2012), whereas another occupational cohort study in Minnesota found no evidence of elevated kidney cancer mortality or incidence among workers highly exposed to ammonium perfluorooctanoate (ammonium salt of PFOA), estimated using air monitoring data (Raleigh et al., 2014). Two studies that included partially overlapping populations were conducted among residents of Mid-Ohio Valley communities exposed to PFOA-contaminated drinking water; both studies reported increased kidney cancer risk associated with higher estimated PFOA serum concentrations, which were predicted using historical PFOA emission data, residential history, and drinking water source and consumption patterns (Vieira et al., 2013; Barry et al., 2013). Taken together, several epidemiologic studies of populations that have experienced relatively high exposures to PFOA support an association between PFOA and RCC risk, and the evidence from studies measuring PFAS concentrations comparable to concentrations observed in the general population is limited to PLCO and the current study and warrants additional research. Additionally, as all previous studies were conducted in populations consisting largely of non-Hispanic White individuals, associations in non-White populations need to be further investigated.

Potential mechanisms through which PFOA may contribute to RCC development include induction of oxidative stress, alterations in inflammatory pathways, suppression of immune function, and modulation of receptor-mediated activity (International Agency for Research on Cancer, 2017; Stanifer et al., 2018; Temkin et al., 2020; Liu et al., 2023). In particular, evidence from human cells *in vitro* and animal experiments suggests that PFOA can promote activation of peroxisome proliferator-activated receptor alpha (International Agency for Research on Cancer, 2017; Stanifer et al., 2018), a nuclear receptor protein involved in lipid metabolism and oxidative stress pathways and has been implicated in nephrotoxicity and renal carcinogenesis (Gan & Gu, 2022; Abu Aboud et al., 2013; Abu Aboud et al., 2015). Moreover, PFOA exposure has been shown to induce renal tubular epithelial hypertrophy or hyperplasia and increased kidney weights in rodent models (Stanifer et al., 2018).

Our study provided novel evidence of a positive association between PFNA and RCC risk, which had the largest effect estimates among African American participants, followed by Native Hawaiian and White participants. This study is the first to present results of PFNA-RCC relationships stratified by race and ethnicity, with statistically significant or suggestive associations observed in both White and non-White individuals. Our previous investigation in PLCO found a suggestive positive association for PFNA (doubling in serum concentration, OR = 1.19, 95 % CI = 0.91, 1.55), although the observed association became null after adjusting for other PFAS (Shearer et al., 2021). Compared to results in PLCO, we observed a stronger association with PFNA in White participants (doubling in serum concentration, OR = 1.98, 95 % CI = 0.92, 4.25), even after adjusting for other PFAS. No other previous studies have examined PFNA-RCC relationships using pre-diagnostic serum samples in the general population. In analyses stratified by calendar year of blood draw, we only observed associations among participants with blood drawn in 2002 or later; this is notable because of the observed increase in PFNA concentrations in the general U.S. population during this time period that was also apparent in our study population (Calafat et al., 2007; Nelson et al., 2012). The association with RCC was also more apparent among cases diagnosed within 7 years of follow-up; whether this reflects PFNA exposure during an etiologically relevant time period for RCC development is unclear, and as such confirmation of these findings for PFNA is needed. PFNA is a suspected genotoxic carcinogen that induces DNA damage. *In vitro* studies reported that exposure to PFNA induced high levels of 8-hydroxy-2-deoxyguanosine, a biomarker of oxidative DNA damage, in human lymphoblastoid cells and increased DNA strand breaks in human hepatoma cells (Yahia et al., 2016; Eriksen et al., 2010; Wielsøe et al., 2015). Some experimental studies reported toxicologic effects of PFNA on kidney health. An animal study of rats demonstrated that prenatal exposure to PFNA resulted in lower renal nephron endowment and elevated blood pressure in offspring (Rogers et al., 2014). Another animal study of male rats observed altered blood plasma levels of diacylglycerols, phosphatidylcholines, and cholesterol derivatives (Skov et al., 2015).

We observed a positive association with RCC for FOSA, which was not measured in the earlier PLCO study. However, this association should be interpreted cautiously given the large proportion of non-detectable concentrations (76 %) and the heterogeneity in effect size in sex-stratified analyses. Notably, serum concentrations of FOSA, a precursor to PFOS, are no longer measured in NHANES because of the high proportion of non-detectable results since the 2003–2004 NHANES cycle (Centers for Disease Control and Prevention), suggesting that FOSA is no longer detected in the majority of the general U.S. population.

We observed an unexpected inverse association between serum PFHxS concentrations and RCC risk, overall and with similar patterns across most racial and ethnic groups. Additionally, while PFOS was not associated with RCC risk overall in our study, statistically significant inverse associations were observed among African American and White participants. Secular trends of declining serum concentrations of PFHxS and PFOS have been observed in the general U.S. population since the early 2000s (Calafat et al., 2007), and concentrations of these PFAS were lower among participants in this study compared with those in PLCO and other studies in highly exposed communities (National Academies of Sciences, Engineering, and Medicine, 2022; Agency For Toxic Substances and Disease Registry). There is limited and inconsistent epidemiologic evidence for the associations of PFHxS and PFOS with kidney cancer risk. In the PLCO cohort, positive associations with RCC risk were observed for both PFHxS and PFOS (doubling in serum concentration, ORs = 1.27 and 1.39, respectively); however, they were attenuated and lost statistical significance in analyses adjusted for other PFAS (Shearer et al., 2021). More recently, in a large Swedish cohort study of individuals who lived in Ronneby, a municipality whose drinking water supplies were historically contaminated with PFAS (predominantly

PFOS and PFHxS) from firefighting foams used at a nearby military airfield, a moderately increased risk of kidney cancer was observed among those who resided in contaminated (vs. uncontaminated) areas (Li et al., 2022). In another study of three Australian communities exposed to PFOS and PFHxS through firefighting foams, elevated incidence of kidney cancer relative to an external comparison population was observed in one but not the other two communities (Law et al., 2023). In light of these findings and mechanistic studies supporting potential roles of PFOS and PFHxS in kidney health and carcinogenesis (e.g., PFOS-induced endothelial permeability through actin filament remodeling) (Stanifer et al., 2018; Temkin et al., 2020; Qian et al., 2010), our findings may be attributable to differences in the magnitude of exposure to these PFAS during etiologically relevant time periods in our study compared with prior studies, or they could also be due to chance.

A strength of this study is that we were able to evaluate the relationship between PFAS and RCC risk in a cohort with greater racial and ethnic diversity than in previous studies, and our investigation included populations that have been understudied with respect to the health effects of PFAS exposures; there is limited epidemiologic evidence related to PFAS and cancer risk in non-White individuals, particularly NHPI and Asian Americans. In addition, NHANES biomonitoring data do not provide PFAS concentrations for NHPI, although information among Asian Americans has been added since the 2011 survey (Centers for Disease Control and Prevention). Other study strengths include our use of pre-diagnostic serum PFAS concentrations, a direct assessment of exposure to specific PFAS, and analyses of individual PFAS, with and without adjustment for other PFAS. We also measured serum creatinine to adjust for kidney function (eGFR) in the analyses. This study also had some limitations. Our analyses stratifying by racial and ethnic groups had limited statistical power. We did not correct for multiple comparisons given *a priori* evidence of associations for some PFAS in previous studies; however, findings due to chance cannot be ruled out, and the associations observed in certain subgroups, particularly those defined by race and ethnicity, require confirmation in future studies. Another limitation is the reliance on PFAS concentrations measured from a single point in time for exposure assessment. In an investigation of intra-individual variability in PFAS concentrations within PLCO (Rhee et al., 2023) using serial samples (baseline, one and five years after baseline), concentrations of most PFAS were consistent (intraclass correlation coefficient > 0.7), suggesting that single-serum measurements are informative surrogates of exposure status across several years. Since nearly all female participants in our study were post-menopausal at blood draw, our findings may not be generalizable to pre-menopausal women whose serum PFAS concentrations are more likely to be affected by menstrual and reproductive factors (Rickard et al., 2022). Lastly, although our analyses adjusted for eGFR as a marker of kidney function, we did not have data on urine or serum albumin levels and were not able to take albuminuria into account. Albuminuria has been associated with lower serum PFAS concentrations, as well as an increased risk of some cancers, possibly including kidney cancer (Jain & Ducatman, 2019; Mok et al., 2020; Jørgensen et al., 2008; Whittemore et al., 1985; Luo et al., 2023). However, it has been reported that the prevalence of albuminuria is higher among individuals with eGFR < 60 compared to those with eGFR ≥ 60 (33 % and 8 %, respectively), and most participants in our study had eGFR ≥ 60 (The United States Renal Data System, 2022). As such, the impact of the lack of adjustment for albuminuria was likely minimal, in particular for those with no evidence of diminished kidney function. We might expect any potential underestimation of true associations between PFAS and RCC to be most apparent among those with low eGFR, as was observed in our stratified analyses of PFOA.

5. Conclusions

In this large nested-case control study of serum PFAS and RCC risk in a racially and ethnically diverse population, PFOA was not associated with RCC risk overall, although we found suggestive positive associations among White participants and those who had blood drawn before 2002, which are consistent with our previous findings in PLCO. We also provided new evidence of a positive association between PFNA and RCC risk, which was strongest in African American participants followed by Native Hawaiian and White participants. Our findings demonstrate the importance for epidemiologic studies to be more inclusive of non-White participants in order to better understand differences in PFAS exposures and their relationships with cancer risk in various racial and ethnic groups.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the U.S. Department of Health and Human Services.

CRediT authorship contribution statement

Jongeun Rhee: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Vicky C. Chang:** Methodology, Formal analysis, Writing – original draft. **Iona Cheng:** Data curation, Methodology, Writing – review & editing. **Antonia M. Calafat:** Data curation, Methodology, Writing – review & editing. **Julianne Cook Botelho:** Data curation, Methodology, Writing – review & editing. **Joseph J. Shearer:** Writing – review & editing. **Joshua N. Sampson:** Writing – review & editing. **Veronica Wendy Setiawan:** Writing – review & editing. **Lynne R. Wilkens:** Data curation, Methodology, Writing – review & editing. **Debra T. Silverman:** Writing – review & editing. **Mark P. Purdue:** Methodology, Supervision, Writing – review & editing. **Jonathan N. Hofmann:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108197.

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Supplementary Table S1. Spearman correlation coefficients of serum PFAS concentrations among controls in the Multiethnic Cohort Study (n=428)

PFAS	PFOA[a]	PFOS[a]	PFHxS	PFNA	PFDA	PFUnDA	MeFOSAA	EtFOSAA	FOSA[b]
PFOA[a]	1.00								
PFOS[a]	0.61	1.00							
PFHxS	0.48	0.55	1.00						
PFNA	0.57	0.48	0.27	1.00					
PFDA	0.48	0.41	0.21	0.84	1.00				
PFUnDA	0.27	0.24	0.08	0.64	0.76	1.00			
MeFOSAA	0.28	0.51	0.28	0.19	0.11	0.12	1.00		
EtFOSAA	0.21	0.49	0.23	−0.07	−0.08	−0.04	0.57	1.00	
FOSA[b]	0.11	0.26	0.08	−0.05	−0.04	−0.01	0.32	0.43	1.00

Abbreviations: EtFOSAA, 2-N-ethyl-perfluorooctane sulfonamido acetate; FOSA, perfluorooctane sulfonamide; MeFOSAA, 2-N-methyl-perfluorooctane sulfonamido acetate; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoate.

[a]PFOA and PFOS here represent the sum of their corresponding linear and branch isomers.

[b]Based on controls with available data on FOSA (n=426; i.e., excluding one control with missing data and another control whose matched case had missing data on FOSA).

Supplementary Table S2. Adjusted geometric least squares means[a] and 95% confidence intervals (CIs) of serum PFAS concentrations among controls in the Multiethnic Cohort Study (n=428)

		N	PFOA[b]	PFOS[b]	PFHxS	PFNA	PFDA	PFUnDA	MeFOSAA	EtFOSAA
Sex										
	Male	268	4.8(3.5-6.7)	33.4(22.5-49.6)	3.5(2.2-5.6)	1.2(0.8-1.6)	0.4(0.3-0.5)	0.3(0.2-0.5)	0.6(0.4-1.0)	0.5(0.3-0.8)
	Female	160	4.7(3.4-6.5)	28.2(19.0-42.1)	2.8(1.8-4.4)	1.1(0.8-1.5)	0.3(0.2-0.5)	0.3(0.2-0.5)	0.5(0.3-0.9)	0.4(0.3-0.7)
	P		0.58	**0.02**	**0.003**	0.08	0.06	0.11	**0.03**	0.55
Race and ethnicity										
	African American	72	4.3(3.1-6.0)	37.5(25.1-56.2)	3.1(1.9-4.9)	1.0(0.7-1.4)	0.4(0.2-0.5)	0.2(0.2-0.4)	0.7(0.5-1.2)	0.4(0.2-0.6)
	Native Hawaiian	50	5.5(3.9-7.8)	34.3(22.3-52.7)	3.1(1.9-5.1)	1.1(0.8-1.6)	0.3(0.2-0.5)	0.3(0.2-0.5)	0.6(0.4-1.0)	0.5(0.3-0.8)
	Japanese	107	4.9(3.5-6.8)	23.8(16.0-35.4)	2.8(1.8-4.4)	1.2(0.8-1.7)	0.4(0.2-0.5)	0.4(0.3-0.7)	0.6(0.4-1.0)	0.4(0.3-0.7)
	Latino	116	3.9(2.8-5.4)	21.5(14.4-32.1)	3.0(1.9-4.8)	0.7(0.5-1.0)	0.2(0.2-0.4)	0.1(0.1-0.2)	0.5(0.3-0.8)	0.3(0.2-0.5)
	White	80	4.9(3.5-6.9)	29.6(19.7-44.7)	3.7(2.3-6.0)	0.8(0.6-1.1)	0.2(0.1-0.3)	0.2(0.1-0.3)	0.5(0.3-0.8)	0.4(0.2-0.7)
	P		0.29	**<.0001**	0.30	**<.0001**	**<.0001**	**<.0001**	**0.01**	0.07
Study center										
	Hawaii	211	4.6(3.3-6.4)	29.5(19.4-44.8)	3.2(2.0-5.1)	1.1(0.8-1.6)	0.4(0.3-0.6)	0.4(0.3-0.7)	0.6(0.4-1.1)	0.4(0.2-0.7)
	California	217	4.9(3.5-6.9)	32.0(21.2-48.3)	3.1(1.9-5.0)	1.1(0.8-1.5)	0.3(0.2-0.4)	0.2(0.1-0.4)	0.5(0.3-0.9)	0.5(0.3-0.9)
	P		0.54	0.57	0.93	0.77	**0.01**	**0.0001**	0.36	0.24
Age at blood draw, years										
	<60	82	5.0(3.6-7.0)	32.4(21.3-49.1)	3.1(1.9-5.1)	1.2(0.9-1.7)	0.4(0.3-0.6)	0.4(0.3-0.6)	0.7(0.4-1.2)	0.4(0.3-0.8)
	60-<65	92	5.1(3.6-7.1)	32.9(21.7-49.9)	3.3(2.0-5.4)	1.2(0.9-1.7)	0.4(0.3-0.6)	0.3(0.2-0.5)	0.6(0.3-0.9)	0.4(0.3-0.8)
	65-<70	91	5.0(3.6-7.0)	32.5(21.6-48.9)	3.0(1.9-4.9)	1.2(0.8-1.7)	0.4(0.3-0.5)	0.3(0.2-0.5)	0.6(0.3-0.9)	0.4(0.3-0.8)
	70-<75	86	4.4(3.1-6.1)	30.5(20.2-46.1)	2.9(1.8-4.6)	1.1(0.8-1.6)	0.3(0.2-0.5)	0.3(0.2-0.5)	0.6(0.3-0.9)	0.4(0.2-0.7)
	≥75	77	4.4(3.1-6.1)	25.9(17.3-38.8)	3.4(2.1-5.4)	0.9(0.6-1.2)	0.3(0.2-0.4)	0.3(0.2-0.4)	0.6(0.3-0.9)	0.5(0.3-0.9)
	P		0.21	0.19	0.69	**0.002**	**0.01**	**0.03**	0.33	0.25
Calendar year of blood draw										
	<2002	91	4.5(3.3-6.2)	38.3(25.9-56.7)	3.4(2.2-5.4)	0.8(0.6-1.1)	0.2(0.2-0.4)	0.3(0.2-0.4)	1.2(0.7-1.9)	2.3(1.4-3.8)
	2002	50	5.6(3.9-8.0)	38.0(24.7-58.6)	3.5(2.1-5.7)	1.0(0.7-1.5)	0.3(0.2-0.5)	0.3(0.2-0.5)	0.7(0.4-1.2)	0.7(0.4-1.3)
	2003	122	4.7(3.4-6.6)	31.8(21.2-47.8)	3.1(1.9-4.9)	1.1(0.8-1.6)	0.4(0.3-0.5)	0.3(0.2-0.5)	0.6(0.4-1.0)	0.3(0.2-0.6)
	2004	106	4.4(3.1-6.1)	26.2(17.4-39.5)	3.1(1.9-5.0)	1.2(0.9-1.8)	0.4(0.3-0.6)	0.3(0.2-0.5)	0.4(0.3-0.7)	0.2(0.1-0.4)
	≥2005	59	4.7(3.3-6.6)	22.5(14.6-34.6)	2.7(1.6-4.4)	1.4(1.0-2.1)	0.5(0.3-0.7)	0.4(0.2-0.6)	0.3(0.2-0.6)	0.1(0.1-0.3)
	P		0.10	**<.0001**	0.44	**<.0001**	**<.0001**	**0.03**	**<.0001**	**<.0001**
Fasting status, hours										
	<10[c]	63	4.9(3.5-6.8)	31.9(21.1-48.4)	3.4(2.1-5.5)	1.2(0.8-1.7)	0.4(0.2-0.5)	0.3(0.2-0.5)	0.6(0.4-1.1)	0.4(0.3-0.8)
	≥10	365	4.6(3.4-6.3)	29.6(20.1-43.5)	2.9(1.9-4.6)	1.1(0.8-1.5)	0.3(0.2-0.5)	0.3(0.2-0.5)	0.5(0.3-0.9)	0.5(0.3-0.8)
	P		0.53	0.43	0.20	0.26	0.48	0.45	0.17	0.67
Hypertension										
	No	229	4.5(3.3-6.2)	30.5(20.6-45.0)	3.0(1.9-4.8)	1.1(0.8-1.5)	0.4(0.2-0.5)	0.3(0.2-0.5)	0.6(0.4-1.0)	0.5(0.3-0.8)

	Yes	199	5.0(3.6-6.9)	31.0(20.8-46.3)	3.2(2.0-5.2)	1.2(0.8-1.6)	0.4(0.2-0.5)	0.3(0.2-0.5)	0.5(0.3-0.9)	0.4(0.2-0.7)
	P		0.09	0.79	0.40	0.21	0.80	0.93	0.05	0.15
Body mass index, kg/m²										
	<18.5	9	5.0(3.3-7.7)	28.2(16.7-47.4)	3.6(2.0-6.6)	1.3(0.8-1.9)	0.4(0.2-0.7)	0.3(0.2-0.5)	0.7(0.4-1.3)	0.5(0.2-1.0)
	18.5-<25	139	5.3(4.2-6.7)	27.0(20.2-36.1)	2.9(2.0-4.0)	0.9(0.7-1.2)	0.3(0.2-0.4)	0.3(0.2-0.4)	0.7(0.5-0.9)	0.4(0.3-0.6)
	25-<30	165	5.5(4.3-7.0)	28.7(21.3-38.7)	3.2(2.3-4.5)	1.0(0.8-1.3)	0.3(0.2-0.4)	0.3(0.2-0.4)	0.7(0.5-1.0)	0.5(0.3-0.7)
	≥30	114	5.4(4.2-6.8)	28.9(21.6-38.8)	2.7(1.9-3.8)	0.9(0.7-1.2)	0.3(0.2-0.4)	0.3(0.2-0.4)	0.7(0.5-1.0)	0.5(0.3-0.7)
	P		0.85	0.88	0.39	0.49	0.29	0.75	0.93	0.87
Smoking status										
	Never	174	4.9(3.6-6.7)	35.0(23.8-51.4)	3.3(2.1-5.1)	1.2(0.9-1.7)	0.4(0.3-0.5)	0.3(0.2-0.5)	0.6(0.4-1.0)	0.5(0.3-0.8)
	Former	181	5.0(3.7-6.8)	33.1(22.7-48.1)	3.4(2.2-5.2)	1.1(0.8-1.6)	0.4(0.3-0.5)	0.3(0.2-0.5)	0.6(0.4-1.0)	0.5(0.3-0.8)
	Current	65	5.1(3.7-7.1)	33.8(22.7-50.4)	3.7(2.3-5.8)	1.2(0.9-1.7)	0.4(0.3-0.5)	0.4(0.2-0.5)	0.5(0.3-0.9)	0.4(0.2-0.7)
	P		0.64	0.33	0.45	0.48	0.93	0.71	0.58	0.79
eGFR, mL/min/1.73 m²										
	<60	116	4.2(3.1-5.6)	26.9(18.7-38.7)	2.6(1.7-4.0)	1.0(0.8-1.4)	0.3(0.2-0.5)	0.3(0.2-0.5)	0.5(0.3-0.8)	0.3(0.2-0.5)
	60-<90	257	4.0(3.1-5.2)	25.8(18.5-35.9)	2.5(1.7-3.7)	1.0(0.7-1.3)	0.3(0.2-0.4)	0.3(0.2-0.5)	0.6(0.4-0.8)	0.3(0.2-0.5)
	≥90	52	4.0(2.9-5.4)	30.0(20.6-43.7)	2.7(1.8-4.2)	1.1(0.8-1.5)	0.3(0.2-0.5)	0.3(0.2-0.5)	0.4(0.3-0.7)	0.4(0.2-0.6)
	P		0.22	0.29	0.30	0.47	0.79	0.91	0.08	0.21
Years since menopause[d]										
	≤10	16	5.2 (3.3-8.3)	18.5 (10.9-31.5)	1.9 (1.0-3.6)	0.8 (0.5-1.3)	0.3 (0.2-0.5)	0.3 (0.1-0.5)	0.3 (0.2-0.7)	0.3 (0.1-0.5)
	>10-15	33	3.8 (2.7-5.6)	18.1 (11.8-27.7)	2.3 (1.4-3.8)	0.9 (0.6-1.3)	0.3 (0.2-0.4)	0.3 (0.2-0.5)	0.4 (0.2-0.7)	0.2 (0.1-0.4)
	>15-20	41	4.5 (3.2-6.3)	18.6 (12.5-27.6)	2.1 (1.3-3.3)	0.8 (0.6-1.2)	0.3 (0.2-0.4)	0.3 (0.2-0.5)	0.3 (0.2-0.5)	0.3 (0.2-0.4)
	>20-25	25	3.8 (2.6-5.6)	18.8 (11.9-29.6)	2.4 (1.4-4.0)	0.8 (0.6-1.3)	0.3 (0.2-0.5)	0.4 (0.2-0.6)	0.5 (0.3-0.9)	0.5 (0.3-0.8)
	>25	34	4.6 (3.1-7.0)	24.8 (15.5-39.7)	2.7 (1.5-4.6)	1.0 (0.7-1.5)	0.3 (0.2-0.5)	0.4 (0.2-0.6)	0.4 (0.2-0.7)	0.4 (0.2-0.7)
	P		0.42	0.65	0.80	0.85	0.99	0.72	0.61	0.09

Abbreviations: EtFOSAA, 2-N-ethyl-perfluorooctane sulfonamido acetate; FOSA, perfluorooctane sulfonamide; MeFOSAA, 2-N-methyl-perfluorooctane sulfonamido acetate; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoate.

[a]Estimated using multivariable linear regression after adjusting for sex, race and ethnicity (African American, Japanese, Latino, Native Hawaiian, White, other), study center (Hawaii, California), calendar year of blood draw (1994-2001, 2002, 2003, 2004, 2005-2006), age at blood draw (<60, 60-<65, 65-<70, 70-<75, ≥75 years), fasting status (<10, ≥10 hours), smoking status (never, former, current, missing), body mass index (<18.5, 18.5-<25, 25-<30, ≥30 kg/m², missing), history of hypertension (yes, no), and eGFR (<60, 60-<90, ≥90+ mL/min/1.73 m², missing).

[b]PFOA and PFOS here represent the sum of their corresponding linear and branch isomers.

[c]Includes fasting <10 hours or unknown.

[d]Among post-menopausal women with no missing data on age at menopause (n=149). Years since menopause were calculated by subtracting age at menopause (estimated as 44, 47, 52, and 55 years for age at menopause categories of <45, 45-49, 50-54, and ≥55 years, respectively) from age at blood draw.

Supplementary Table S3. Odds ratios (ORs)[a] and 95% confidence intervals (CIs) evaluating quartiles of PFAS serum concentrations and risk of renal cell carcinoma stratified by race and ethnicity in the Multiethnic Cohort Study

	African American			Japanese			Latino			Native Hawaiian			White		
	N control	N case	OR (95% CI)	N control	N case	OR (95% CI)	N control	N case	OR (95% CI)	N control	N case	OR (95% CI)	N control	N case	OR (95% CI)
PFOA															
≤3.27	21	24	1	24	14	1	37	38	1	5	12	1	18	19	1
>3.27-4.47	17	15	1 (0.23,4.33)	24	25	2.62 (0.79,8.69)	28	33	1.57 (0.7,3.52)	12	10	0.3 (0.04,2.31)	20	15	2.08 (0.62,6.98)
>4.47-6.22	16	17	1.01 (0.24,4.23)	35	37	2.65 (0.77,9.15)	30	26	1.13 (0.45,2.86)	15	17	0.28 (0.03,2.39)	17	24	3.63 (0.84,15.8)
>6.22	18	16	1.08 (0.23,5.13)	24	31	3.29 (0.84,12.88)	21	19	1.12 (0.35,3.62)	18	11	0.08 (0.01,0.94)	25	22	2.94 (0.56,15.5)
P-trend	72	72	0.91	107	107	0.22	116	116	0.96	50	50	**0.04**	80	80	0.48
PFOS															
<16.65	4	12	1	30	28	1	38	42	1	9	11	1	26	25	1
16.65-<25.05	9	14	0.16 (0.02,1.45)	34	29	1.39 (0.51,3.79)	39	31	1.12 (0.46,2.68)	10	7	0.59 (0.06,5.4)	15	23	1.87 (0.48,7.3)
25.05-<36.40	20	12	0.03 (0,0.35)	26	26	1.62 (0.44,6.01)	25	32	2.58 (0.9,7.39)	12	19	1.66 (0.26,10.49)	22	10	0.24 (0.05,1.15)
≥36.40	39	34	0.03 (0,0.36)	17	24	2.49 (0.59,10.55)	14	11	1.6 (0.36,7.04)	19	13	0.04 (0,0.83)	17	22	1.39 (0.21,9.18)
P-trend	72	72	**0.02**	107	107	0.22	116	116	0.25	50	50	0.07	80	80	0.77
PFHxS															
<1.6	14	18	1	35	25	1	25	38	1	14	12	1	17	28	1
1.6-<2.4	15	16	0.89 (0.16,5.01)	26	35	1.71 (0.7,4.16)	35	30	0.47 (0.19,1.15)	11	16	1.9 (0.37,9.66)	15	16	0.26 (0.07,1)
2.4-<3.55	22	17	0.56 (0.11,2.84)	28	26	0.95 (0.38,2.35)	32	23	0.29 (0.11,0.79)	12	9	0.56 (0.07,4.7)	17	13	0.27 (0.06,1.15)
≥3.55	21	21	0.73 (0.12,4.44)	18	21	1.04 (0.31,3.46)	24	25	0.58 (0.18,1.81)	13	13	1.17 (0.2,6.85)	31	23	0.27 (0.06,1.16)
P-trend	72	72	0.76	107	107	0.76	116	116	0.80	50	50	0.84	80	80	0.36
PFNA															
≤0.5	19	21	1	16	12	1	51	52	1	8	9	1	37	25	1
>0.5-0.8	22	16	1.71 (0.39,7.43)	20	27	1.95 (0.44,8.64)	43	40	1.21 (0.52,2.84)	11	12	1.49 (0.22,9.97)	24	17	0.83 (0.2,3.46)
>0.8-1.1	18	16	2.52 (0.47,13.63)	29	21	1.03 (0.23,4.7)	15	15	1.59 (0.52,4.84)	13	8	0.55 (0.08,4.06)	9	18	5.33 (0.78,36.27)
>1.1	13	19	9.65 (1.15,80.89)	42	47	1.65 (0.27,10.09)	7	9	2.64 (0.61,11.49)	18	21	0.96 (0.1,9.74)	20	20	2.55 (0.36,17.86)
P-trend	72	72	**0.02**	107	107	1.00	116	116	0.17	50	50	0.83	80	80	0.39

Abbreviations: PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate.

[a]Analyses were conducted using conditional logistic regression models of matched case-control sets adjusting for smoking status (never, former, current, missing), body mass index (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2, missing), history of hypertension (yes, no), estimated glomerular filtration rate (<60, 60-<90, ≥90 mL/min/1.73 m^2, missing), PFOA (log2-transformed), PFOS (log2-transformed), PFHxS (log2-transformed), PFNA (log2-transformed), FOSA (non-detectable, detectable, missing).

[b]PFOA and PFOS here represent the sum of their corresponding linear and branch isomers.

Bold indicates statistical significance at P<0.05.

Supplementary Table S4. Odds ratios (ORs) and 95% confidence intervals (CIs) evaluating PFAS serum concentrations and risk of renal cell carcinoma stratified by additional selected characteristics in the Multiethnic Cohort Study

Characteristic	N controls	N cases	PFOA[a]	PFOS[a]	PFHxS[a]	PFNA[a]	FOSA[a]
All[b]	428	428	0.89 (0.67,1.18)	0.95 (0.74,1.23)	**0.82 (0.69,0.98)**	1.29 (0.97,1.71)	**1.78 (1.05,3.04)**
History of hypertension[c]							
No	229	183	1.20 (0.79,1.85)	0.76 (0.51,1.12)	0.97 (0.76,1.23)	1.38 (0.95,2.00)	1.23 (0.71,2.11)
Yes	199	245	0.77 (0.53,1.12)	1.03 (0.72,1.48)	**0.72 (0.57,0.92)**	**1.50 (1.06,2.12)**	1.35 (0.80,2.29)
P-interaction[d]			0.12	0.80	0.05	0.83	0.85
Smoking[c]							
Never	174	188	1.33 (0.86,2.05)	0.78 (0.51,1.17)	0.85 (0.65,1.12)	1.18 (0.79,1.75)	1.76 (0.96,3.22)
Ever	246	231	0.80 (0.56,1.16)	0.87 (0.61,1.24)	0.89 (0.71,1.11)	**1.43 (1.02,2.00)**	1.14 (0.69,1.89)
P-interaction[d]			0.13	0.55	0.98	0.80	0.68
BMI[c]							
<25	148	115	1.00 (0.60,1.69)	1.07 (0.69,1.65)	0.81 (0.60,1.10)	1.00 (0.63,1.58)	1.36 (0.70,2.65)
25-<30	165	194	1.01 (0.65,1.56)	0.86 (0.56,1.33)	0.93 (0.71,1.20)	1.25 (0.84,1.85)	1.07 (0.61,1.86)
≥30	114	117	0.72 (0.40,1.30)	0.63 (0.35,1.14)	0.81 (0.56,1.18)	**2.15 (1.25,3.71)**	1.94 (0.82,4.45)
P-interaction[d]			0.66	0.90	0.37	0.41	0.42
Fasting status[b]							
<10 hours[e]	63	63	0.50 (0.17,1.46)	1.53 (0.47,5.04)	0.55 (0.25,1.20)	0.36 (0.10,1.29)	**18.96 (1.87,192.07)**
≥10 hours	365	365	0.87 (0.64,1.19)	0.88 (0.67,1.16)	0.83 (0.69,1.00)	**1.58 (1.15,2.17)**	**1.89 (1.03,3.45)**
P-interaction[d]			0.14	0.16	0.12	**0.005**	0.77
RCC subtype[b]							
Clear cell RCC	255	255	0.97 (0.64,1.47)	0.97 (0.67,1.39)	0.85 (0.67,1.07)	1.13 (0.79,1.61)	1.34 (0.63,2.87)
Excluding first two years of follow-up[b]	376	376	0.93 (0.69,1.27)	1.00 (0.74,1.35)	**0.79 (0.65,0.96)**	1.25 (0.92,1.69)	**1.83 (1.03,3.26)**
Excluding participants with a history of cancer prior to blood collection[c]	351	353	1.03 (0.77,1.39)	0.79 (0.59,1.06)	0.83 (0.70,1.00)	**1.35 (1.02,1.77)**	1.43 (0.93,2.21)
Excluding participants with missing data on BMI, smoking, and/or eGFR[b]	404	404	0.86 (0.64,1.16)	0.95 (0.73,1.24)	0.84 (0.71,1.01)	1.30 (0.97,1.73)	**1.99 (1.15,3.43)**

Restricting to female participants with >10 years since menopause[c,f]	133	127	0.86 (0.53,1,40)	0.98 (0.63,1.51)	0.78 (0.57,1.07)	1.45 (0.94,2.22)	**2.62 (1.21,5.65)**

Abbreviations: FOSA, perfluorooctane sulfonamide; PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate

[a]Continuous odds ratios (95% confidence intervals) for renal cell carcinoma in relation to a 1-unit increase in serum PFAS concentrations on the log base 2 scale, corresponding to a doubling in analyte concentrations. For FOSA analysis, ORs for detectable FOSA vs. non-detectable FOSA are presented. PFOA and PFOS here represent the sum of their corresponding linear and branch isomers

[b]Analyses were conducted using conditional logistic regression models of matched case-control sets adjusting for smoking status (never, former, current, missing), body mass index (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2, missing), history of hypertension (yes, no), eGFR (<60, 60-<90, ≥90 mL/min/1.73 m^2, missing), PFOA (log2-transformed), PFOS (log2-transformed), PFHxS (log2-transformed), PFNA (log2-transformed), and FOSA (non-detected, detected, missing).

[c]Analyses were conducted using unconditional logistic regression models adjusting for sex, race and ethnicity (African American, Japanese, Latino, Native Hawaiian, White, other), study center (Hawaii, California), calendar year of blood draw (1994-2001, 2002, 2003, 2004, 2005-2006), age at blood draw (<60, 60-<65, 65-<70, 70-<75, ≥75), fasting (≥10 hour, <10 hour or missing), smoking status (never, former, current, missing), body mass index (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2, missing), history of hypertension (yes, no), eGFR (<60, 60-<90, ≥90 mL/min/1.73 m^2, missing), PFOA (log2-transformed), PFOS (log2-transformed), PFHxS (log2-transformed), PFNA (log2-transformed), and FOSA (non-detectable, detectable, missing). For FOSA, we used matched case-control sets for analyses (426 cases, 426 controls).

[d]Wald tests were conducted to calculate P-interaction.

[e]Includes fasting <10 hours or unknown.

[f]Years since menopause were calculated by subtracting age at menopause (estimated as 44, 47, 52, and 55 years for age at menopause categories of <45, 45-49, 50-54, and ≥55 years, respectively) from age at blood draw.

Bold indicates statistical significance at P<0.05.

Supplementary Table S5. Odds ratios (ORs) and 95% confidence intervals (CIs) evaluating PFNA serum concentrations and risk of renal cell carcinoma additionally adjusting for PFDA and PFUnDA, overall and stratified by race and ethnicity in the Multiethnic Cohort Study

Characteristic	N controls	N cases	OR (95% CI)[a]	OR (95% CI)[b]
All	428	428	1.29 (0.97,1.71)	1.24 (0.88,1.75)
Race and ethnicity				
African American	72	72	**3.69 (1.33,10.25)**	**3.62 (1.20,10.93)**
Japanese	107	107	0.82 (0.41,1.61)	0.77 (0.33,1.82)
Latino	116	116	1.03 (0.56,1.89)	0.84 (0.40,1.80)
Native Hawaiian	50	50	2.24 (0.70,7.19)	2.98 (0.63,14.10)
White	80	80	1.98 (0.92,4.25)	1.71 (0.69,4.22)
P-interaction[c]			0.96	0.92

Abbreviations: FOSA, perfluorooctane sulfonamide; PFDA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFUnDA, perfluoroundecanoate.

[a]Analyses were conducted using conditional logistic regression models of matched case-control sets adjusting for smoking status (never, former, current, missing), body mass index (<18.5, 18.5-<25, 25-<30, ≥30 kg/m^2, missing), history of hypertension (yes, no), eGFR (<60, 60-<90, ≥90 mL/min/1.73 m^2, missing), serum concentrations of PFOA (log2-transformed), PFOS (log2-transformed), PFHxS (log2-transformed), PFNA (log2-transformed), FOSA (non-detectable, detectable, missing). Continuous odds ratios (95% confidence intervals) for renal cell carcinoma in relation to a 1-unit increase in serum PFAS concentrations on the log base 2 scale, corresponding to a doubling in analyte concentrations.

[b]Additionally adjusted for serum concentrations of PFDA (log2-transformed) and PFUnDA (log2-transformed).

[c]Wald tests were conducted to calculate P-interaction.

Bold indicates statistical significance at P<0.05.